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DECLARATION OF JAMES R. SCHNEIDER, M.D. UNDER 37 C.F.R. § 1.132	Attorney Docket No.	SNDR-001CIP
	Confirmation No.	5537
	First Named Inventor	SCHNEIDER, JAMES R.
	Application Number	09/307,956
	Filing Date	May 10, 1999
	Group Art Unit	3738
	Examiner Name	David J. Isabella
	Title: "PRESERVED INPLANTABLE VESSEL DERIVED FROM A HUMAN UMBILICAL CORD OR PLACENTA"	

Dear Sir:

1. I, James R. Schneider, M.D. declare and say I am a resident of the State of California.

2. I hold a M.D. degree which I received from University of Iowa. I also hold a Bachelor's degree in Sociology/Psychology which I received from Drake University.

3. I am the inventor of the claimed invention in the above-referenced patent application. The claims are directed to allografts comprising preserved vessels, which preserved vessels are isolated from a human umbilical cord

4. I have reviewed the Office Action mailed May 7, 2003 in the above-referenced application. I understand that the claims are rejected as being obvious in view of the combined references of 1) Pratt et al. (Laryngoscope 1986 96(6):625-9; 29th Ann. Meeting of Amer Society for Head and Neck Surgery) ("Pratt") and Dardik et al. (US 3,974,526) ("Dardik"); or 2) Pratt, Dardik, Lau et al. (US 5,876,432) ("Lau") and Chin et al. (US 5,800,540) ("Chin").

THE REFERENCES OF PRATT, DARDIK, LAU, AND/OR CHIN DO NOT LEAD ONE TO EXPECT THAT FREEZE-DRIED VESSELS PREPARED FROM HUMAN UMBILICAL CORD OR PLACENTA HAVE SUFFICIENT INTEGRITY TO BE USEFUL AS GRAFTS

5. It can not be predicted from the combined references of Pratt, Dardik, Lau and Chin whether a freeze-dried vessel prepared from a human umbilical cord vessel or a placental vessel would work as a graft in a non-fetal human.

6. Vessels of human placenta and umbilical cord are quite delicate. For example, the umbilical cord vessels are surrounded by a protective sheath of tissue so as to prevent damage or collapse of the vessels. Because the vessels are delicate, it was not known whether removal of umbilical cord or placental vessels followed by freeze-drying would so badly damage the vessels so as to render them useless. The freeze-drying process could very well have destroyed the integrity of the vessels.

7. In addition, fetal blood pressure is usually in the range of about 60/25 mmHg. In contrast, blood pressure in a healthy adult is about 140/80 mmHg. Placental and umbilical cord vessels in nature are subjected to less than about *half* of the pressure to which adult vessels are subjected. Moreover, blood pressure in adults with hypertension or malignant hypertension (those who would likely receive an endovascular graft) is even higher – about 160/90 and 180/120, respectively. It could not have been predicted that the integrity of placental or umbilical cord vessels would be maintained after freeze-drying. Similarly, there was no reasonable expectation that *freeze-dried* vessels could be used in an adult graft and withstand *at least twice or more the blood pressure* than that to which the fresh tissue is subjected in nature.

COMMENTS ON STATEMENTS IN PRATT REFERENCE REGARDING FUTURE STUDIES

8. The rejections in the Office Action rely primarily upon Pratt et al. (Laryngoscope 1986 96(6):625-9; 29th Ann. Meeting of Amer Society for Head and Neck Surgery) (the "Pratt reference"). I am a co-author of this paper along with Pratt and Galey.

9. The Office Action states that the Pratt reference suggests that freeze-dried vessels should be explored as microarterial allografts. The statement to which the Office Action refers is as follows:

> Eventually, it is anticipated that freeze-dried placental or donor vessels could be used in clinical trials *if future preliminary laboratory studies in rabbits and larger animals are successful.*

(Pratt reference, page 11, last full paragraph; emphasis added)

10. This statement in the Pratt reference is merely a wishful statement. At best it is a suggestion to try use of freeze-dried placental vessels. There is nothing in the Pratt reference or in the art at the time the present application was filed to provide any certainty that a freeze-dried placental vessel or a freeze-dried umbilical cord vessel would have sufficient integrity to withstand blood pressure of a non-fetal human (e.g., a human adult).

STUDIES DEMONSTRATING INTEGRITY OF FREEZE-DRIED UMBILICAL CORD AND PLACENTAL VESSELS

11. The following experiments were conducted by me or under my direction.

1) Human Umbilical Vessel Pressure Studies

12. Two umbilical cord/placenta units were obtained. At the time of delivery of the baby, the units were rinsed externally with saline and placed in refrigeration in moistened condition. The units were then utilized in the laboratory within six hours of delivery. Unit A weighed 567 grams, with the umbilical cord measuring 59 cm. Unit B weighed 610 grams, with the umbilical cord measuring 54 cm.

13. Each umbilical cord was incised transversely, proximal to the placenta, with separation from the placentas. The umbilical vessels ends were identified, permitting irrigation of each vessel with heparin and saline.

14. Small (2 mm) urologic catheters were then inserted into each vessel. The colored catheters provided easy identification of the umbilical vessels and facilitated handling of the vessels during dissection. The vessels were then removed from the cord by blunt-dissection technique, to minimize trauma to the vessel walls. The catheters were removed from the vessels. The vessels from Unit A were used for initial pressure testing. The vessels from Unit B were set aside to carry out pressure testing following freeze drying. Each vessel from Unit A was placed on a cannula with a ridged tip, and clamped to the cannula, which was attached to the modified heart pump. Saline was then introduced into the vessel, to distend the vessel and to exclude air. The distal end of the vessel was then clamped and triple ligated.

15. The vessels were placed at a steady 120 mmHg pressure, and then were pulsed at 120/80 mmHg. Following this, the pressure was gradually increased to 160/120 mmHg pressure to equal the maximum level of human hypertension. There was no aneurysm formation or vessel wall rupture. One artery slipped off the cannula at 150 mmHg due to the connection, rather than to vessel wall failure.

16. The vessels were re-irrigated with heparinized saline, and placed in a freeze dry canister. They were found to be of widened external diameter (4 mm), compared to the untested vessels (3 mm). The untested vessels from Unit B were place in a separate freeze dry canister. Both canisters were then freeze dried.

17. Three days later, each vessel was removed from the containers, hydrated, and placed into the pressure testing format previously used prior to freeze-drying. Each vessel successfully demonstrated vessel wall integrity. Following this testing sequence, the widths of the vessels had equal external diameter (4 mm).

18. This study successfully demonstrated the capability for umbilical vessels, isolated from the umbilical cord, to sustain blood pressures equal to that level being present in adults.

2) Canine Umbilical Cord Vessel Pressure Study

19. In preparation for a large animal phase of freeze dried implants, a canine umbilical cord/placental unit was obtained following delivery of multiple Labrador retriever pups. The cord unit was irrigated with saline and placed in refrigeration under moistened condition. Within 24 hours of delivery, the cord unit was utilized in the laboratory.

20. Three canine umbilical cords were selected and were incised transversely, proximal to the placenta. The umbilical veins were identified and irrigated with heparinized saline. The umbilical cord sheath was then incised longitudinally, at which time the umbilical vein from each cord was isolated. With the small size of the umbilical cords, and the minute (0.75 mm) internal diameter of the veins, working with the umbilical veins was difficult.

21. One umbilical vein was placed over a cannula tip, and was tested with a blood pressure bulb to 140 mmHg pressure. There was no aneurismal formation or loss of vessel wall integrity. The tested vein was then removed from the apparatus and freeze dried, along with the two untested veins.

22. One week later, the vessels were removed from the canister and re- hydrated with heparinized saline. The previously tested vein and one untested vein were then placed on the apparatus with identical testing method. No vessel wall aneurysm or rupture occurred.

3) Bovine Umbilical Cord Vessel Pressure Study

23. Two bovine umbilical cord/placenta units were obtained from a nearby ranch. The units were rinsed with tap water after calf delivery, then placed in refrigeration in

moistened condition. Each unit was utilized in the laboratory within 12 hours of calf delivery.

24. The umbilical cords were incised transversely, proximal to the placenta. The umbilical veins were identified, being 2 mm internal diameter and were irrigated with heparinized saline. Each umbilical cord was then incised longitudinally, and the umbilical vein was removed.

25. One vein was then tested, utilizing a modified heart pump, to provide steady 120 mmHg pressure. The vein was pulsed to 120/80 mmHg. No loss of vessel wall integrity was present. The tested and untested umbilical veins were then placed in a freeze dry canister.

26. Following freeze drying, the vessels were each tested in an identical manner. The vessels demonstrated maintenance of vessel wall integrity.

4) Human Umbilical Vessel Pressure and Radiographic Studies (1995)

27. Three human umbilical cords/placental units were made available at Tahoe Forest Hospital, Truckee, California. At the time of infant delivery, the units were irrigated externally with saline, and refrigerated, maintaining their moist condition. The umbilical/placental units were utilized in the laboratory within six hours of infant delivery. Each umbilical/placental unit was rinsed with heparinized saline.

28. Unit A weighed 520 grams, with cord length of 61 cm. The umbilical cord was incised transversely proximal to the placenta. The umbilical vessels were irrigated with heparinized saline.

29. The other two units were prepared with the goal of maintaining the umbilical vessel entry into the placenta. Unit B weighed 572 grams, with cord length of 59 cm. Unit C weighed 538 grams with cord length of 56 cm.

30. Each umbilical cord was then incised longitudinally, exposing the vessels and Wharton's Jelly. Hyaluronidase was used to denature the Wharton's Jelly, to further facilitate the removal of the vessels from the cord. Each vessel was cannulated with a 3 mm urologic catheter, being left in the vessels during isolation of each vessel. Blunt dissection was utilized to minimize potential vessel wall injury from sharp dissection methods. The catheters were then removed.

31. The umbilical vein and one umbilical artery from Unit A were set aside for anatomical and radiographic study.

32. Units B and C were further prepared by dissecting the placental vessels in continuity with the umbilical cord vessels. Thus, two veins and four arteries were obtained, each being 26 cm (10 inches) long. The umbilical cord portion was 20 cm (8 inches) long, in continuity with the placental vessel extensions of 5 cm (2 inches) long. The vessels of Unit B were instilled with heparinized saline, to full normal dilation. The distal ends of the placental vessels were ligated.

33. A modified heart pump produced sustained blood pressure of 120 mmHg. Pressure was then pulsed to provide 120/80 mmHg pressure, with pulse rate varying from 60 to 110 pulses per minute. Each blood vessel being tested was pinched, was kinked and torqued with no loss of vessel wall integrity. The pressure was then increased to 140/90 mmHg, similar to that pressure seen in adult hypertension. The pressure was further increased to 150/120 mmHg, in essence the maximum pressure beyond which a lethal condition would be endured by a patient.

34. It is noted that following testing of Unit B vessels (one umbilical vein and two arteries), that the vessels were dilated to a 4 mm internal diameter. The three tested vessels from Unit B and three untested vessels from Unit C were then freeze dried.

35. Following freeze drying, the vessels were reconstituted with saline. All six vessels were tested in the manner previously described. No loss of vessel wall integrity was

encountered. Following testing, all vessels demonstrated the expanded internal diameter of 4 mm.

36. It was concluded that freeze dried umbilical and placental vessels are capable of functioning at adult pressures, resisting rupture or aneurysm.

Conclusion

37. The studies above demonstrate that umbilical cord and placental vessels can be preserved by freeze-drying according to the invention and maintain sufficient integrity to be useful as grafts in a human adult.

38. I, James R. Schneider, M.D., hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

January 28, 2005
Date

James R. Schneider, M.D.
James R. Schneider, M.D.